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A Library Construction of 2,5-Disubstituted Pyrrole Compounds by Using Solid/Solution-Phase Syntheses

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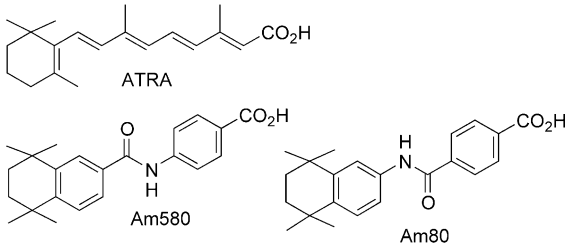
Abstract—Using solid- and solution-phase synthesis, a library of 2,5-disubstituted pyrrole compounds was constructed. This is the first report that Stetter reaction was applied to the solid-phase synthesis for C–C bond formation. Some of 2,5-disubstituted pyrrole compounds showed the inhibitory activity of LPS-induced mouse B-lymphocyte proliferation.

Introduction

Retinoids, natural and synthetic analogues of all-trans retinoic acid (ATRA), have a variety of potent biological activities, including induction of cellular proliferation, differentiation and apoptosis, as well as developmental changes.[1] It has been shown that the biological effects of retinoids are mediated by the activation of retinoic acid receptors (RARs), which are ligand-dependent gene transcription factors. There are three distinct receptor subtypes (RARα, β, and γ), which possess considerable homology in their ligand binding domains.[2]

Although retinoids are thought to have great therapeutic potential, the clinical use of retinoids is so far limited mainly to dermatological diseases[3] and some cancers, in which retinoids may have both chemotherapeutic and chemopreventive applications.[4] The main reason for this could be the wide range of toxic effects of retinoids.[5] Severe toxicity is thought to be caused by the non-specific activation of nuclear retinoid receptor subtypes, so subtype-specific retinoids might have limited biological activities through activating only subsets of retinoid-responsive genes. Thus, recent research has focused on the synthesis and development of subtype-selective retinoids in order to reduce the toxicity.[6]

Only a few of RARα agonists have been reported so far. Apfel et al. reported that the RARα agonist Ro 40–6055 (Am580) was a potent inhibitor of LPS-induced murine B-lymphocyte proliferation and that there was a correlation between the activity of RARα transcription and its potency to inhibit B-cell activation.[7] Am80 is more potent than ATRA as an in vitro differentiation inducer, and inhibited rat CII-induced arthritis.[8] Moreover, this compound was clinically effective on leukemia patients[9] and psoriasis patients.[10] Therefore, RARα agonists seemed to be promising compounds for the treatment of cancer, dermatological diseases, and immunological disorders.



In the course of our studies to synthesize novel retinoid analogues,[11] Nagai et al. have already reported that 2,5-disubstituted pyrrole derivatives were the selective

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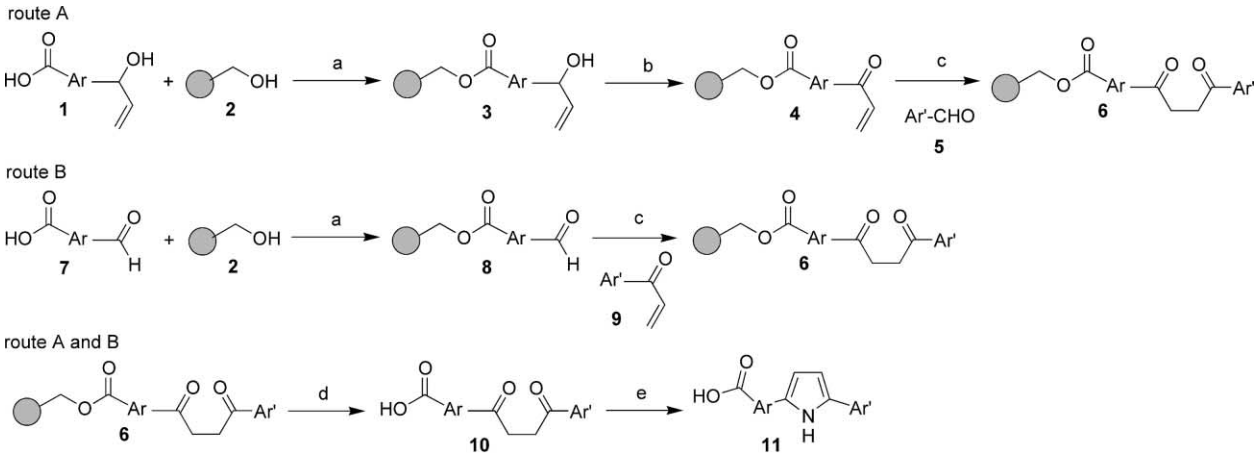

Scheme 1. Reagents and conditions: (a) diisopropylcarbodiimide (DIC), *N*,*N*-dimethylaminopyridine, 3:1 CH_2Cl_2–DMF, rt, 24 h; (b) Dess–Martin reagent, DMF, rt, 4 h; (c) aldehyde (**5**) for route A, enone (**9**) for route B, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride, Et_3N, DMF, 65 °C, 3 h; (d) TFA, CH_2Cl_2; (e) NH_4OAc, MeOH, 70 °C 15 h, then water, filtration.

RARα agonists.[12] Therefore, it was thought that the construction of 2,5-disubstituted pyrrole library using combinatorial approach might be useful for the discovery of potent selective RARα agonists. Here we report the solid- and solution-phase syntheses of 2,5-diarylpyrroles and their inhibitory activity of LPS-induced murine B-lymphocyte proliferation.

Retrosynthetic Analysis

Solid-phase synthesis is now widely used to synthesize a variety of small organic molecules. However, the development of C–C bond formation on solid support is still important. Stetter reaction is one of the best methods to form 1,4-diketone from aldehyde and α,β-unsaturated ketone, where C–C bond formation is included.[13] Since 2,5-disubstituted pyrrole is easily synthesized from 1,4-diketone, we examined to apply Stetter reaction to solid phase synthesis. To maximize the diversity of substituents of pyrrole, two ways for attaching compounds to resin were considered for development — charging a solid support with formylaryl acid or acryloylaryl acid, followed by Stetter reaction, cleavage, and cyclization with ammonium should readily provide the accessible route to a 2,5-disubstituted pyrrole library.

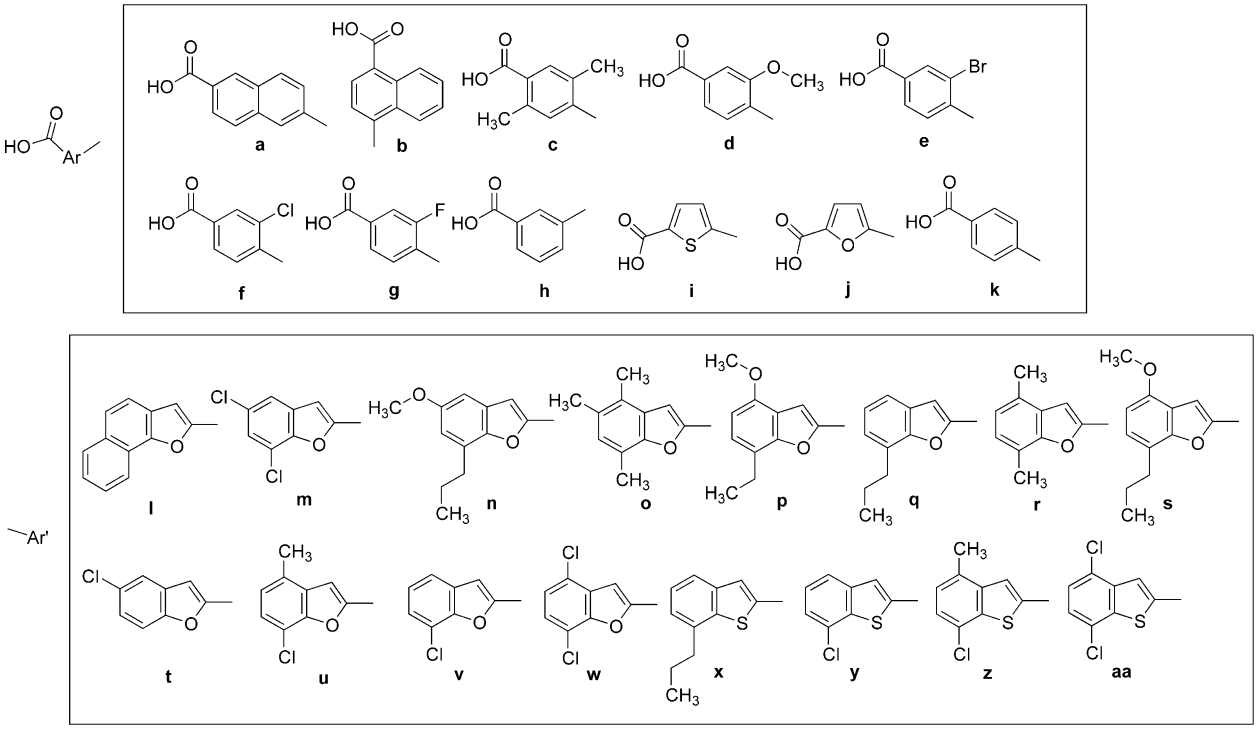

Figure 1.

Table 1. LPS-induced mouse B-cell proliferation inhibition

Compd (**11**)[a]	Relative IC_{50}[b]	Compd (**11**)[a]	Relative IC_{50}[b]
a–o	—[c]	**e–u**	16
a–p	—[c]	**e–v**	31
a–q	—[c]	**e–w**	45[d]
a–r	—[c]	**f–r**	23
a–s	—[c]	**f–v**	300
a–u	—[c]	**f–w**	240
a–aa	—[c]	**g–r**	15
b–o	—[c]	**g–v**	95
b–p	—[c]	**g–w**	64
b–r	—[c]	**h–r**	2100
b–s	—[c]	**h–y**	—[c]
b–t	—[c]	**i–o**	230
b–x	—[c]	**i–p**	—[c]
b–z	—[c]	**I–r**	42
b–aa	—[c]	**i–s**	—[c]
c–m	—[c]	**i–t**	—[c]
c–n	—[c]	**i–w**	62
c–o	—[c]	**i–x**	600
c–p	—[c]	**i–z**	480
c–q	—[c]	**j–o**	—[c]
c–r	—[c]	**j–p**	—[c]
c–s	—[c]	**j–r**	—[c]
c–t	—[c]	**j–s**	—[c]
d–r	47	**j–t**	—[c]
d–v	170	**k–o**[e]	2.2 (±0.5)[e]
d–w	210	**k–r**[e]	0.76 (±0.28)[e]
e–l	1500	**k–w**[e]	1.3 (±0.4)[e]
e–o	42	ATRA	1.0
e–p	140	ATRA[f]	0.65±0.10[f]
e–r	18		

[a]See Figure 1 for identities of partial structures.
[b]Relative IC_{50} = IC_{50}/ATRA IC_{50}.
[c]— = not detectable (relative IC_{50} > 1000).
[d]Values are means of two experiments.
[e]Reported in ref 12c.
[f]Means of ATRA IC_{50} (nM)±SEM.

Chemistry

Two alternative routes for the synthesis of the pyrrole derivatives are shown in Scheme 1. The (1-hydroxyallyl)aryl carboxylic acids (**1**) were attached to Wang polystyrene resin (**2**) using DIC. Oxidation of the resulting resin bound alcohol (**3**) by Dess–Martin reagent gave the enone (**4**). Stetter reaction of the enone (**4**) with the aldehydes (**5**) on solid support successfully gave the 1,4-diketones (**6**) (route A). The formylaryl carboxylic acids (**7**) were attached to Wang polystyrene resin in the same manner (route B). Stetter reaction of the solid-supported aldehydes (**8**) with the enones (**9**) also successfully gave the 1,4-diketones (**6**). Treatment of the resin with TFA in CH_2Cl_2 afforded 1,4-diketones (**10**) bearing carboxylic acid. Cyclization of the 1,4-diketones (**10**) with ammonium acetate gave the desired pyrrole compounds (**11**). The isolation of most pyrroles (**11**) was easily performed by the filtration after addition of water. However, some compounds needed to be extracted with ethyl acetate.

Results and Discussion

Stetter reaction successfully proceeded in both cases of solid-supported aldehydes and solid-supported enones. Aryl moieties used in the reactions are shown in Fig 1. Note that not all the combinations were prepared. The compounds actually prepared are listed in Table 1. The purity of final pyrrole compounds was determined by ^{1}H NMR spectra. It was more than 80% for precipitated compounds, however the purity of some extracted compounds was about 50%. We assumed that it was high enough for the biological assay. Therefore no further purification was done. The compounds were evaluated for their inhibition of LPS-induced mouse B-lymphocyte proliferation in the method reported by Apfel,[7] and the results are also summarized in Table 1.

All these compounds showed weaker inhibitory activity than compounds having no substituents on benzoic acid moiety (data not shown). The introduction of the small substituents into the meta position of benzoic acid resulted in 10- to 200-fold decrease in the activity. The substitution of para-benzoic acid by thenoic acid still showed weak activity, however, the substitution of para-benzoic acid by meta-benzoic acid, naphthoic acid, and furoic acid lost the activity. 2,5-Disubstituted benzoic acid also lost the activity.

In conclusion, we have developed the construction of a 2,5-disubstituted pyrrole library. It was found that Stetter reaction was applicable to the solid supported enones and/or aldehydes. Some of synthesized compounds showed the inhibitory activity of LPS-induced mouse B-lymphocyte proliferation. A synthesized compound showed selective but weak binding affinity for RAR α over RAR β and RAR γ.[14]

This paper demonstrates that the present method is an efficient way for the SAR study of pharmacological activities as well as the useful route for the C–C bond formation of solid-phase synthesis.

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14. Binding affinity as relative IC_{50} of compound (**11e**–**u**) was 238, >1562 and >1000 for RARα, RARβ and RARγ, respectively. Binding assays for RAR receptor subtypes were performed in a manner similar to that described previously[12(d)] using [^{3}H] ATRA. Specific binding affinity was defined as total binding minus nonspecific binding, and the 50% inhibitory dose (IC_{50}) values were obtained from logarithmic plots. The selectivity of the compound for each receptor is indicated as relative IC_{50}, where the IC_{50} value for each receptor was divided by that of the natural ligand (ATRA).